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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,300	10/26/2001	Steven E. Ealick	UAB-20702/22	2920

7590 02/10/2005

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,300	EALICK ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,9-33,54 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *54 and 56* is/are allowed.

6)☒ Claim(s) *1,2,6,7,9-33,54 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 11/12/04. The amendment has been entered. Claims 1, 2, 6, 7, 9-33, 54 and 56 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Objections

Claim 30 is objected to because of the following informalities: it appears that claim 30 contains a typographical error. Specifically, claim 30 recites, "the nucleotide sequence is comprising residues 1-720..." (Emphasis added). As written, the claim is grammatically incorrect. Amending the claim to recite, "the nucleotide sequence comprises residues 1-720..." would obviate this objection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite because it depends on claim 4, which has been cancelled.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7 and 9-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The new limitation "full length mutant microbial purine nucleoside phosphorylase" is considered to be new matter as the specification only discloses full-length mutant E. coli purine nucleoside phosphorylases.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, the instant claims are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most

nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 states:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

The instant claims are drawn to an isolated nucleotide sequence comprising a coding sequence for a full length mutant microbial purine nucleoside phosphorylase (PNP) having an amino acid substitution, wherein the mutant PNP has different biological activity than a wild type microbial PNP, as well as a vector comprising the isolated nucleotide sequence, a host cell comprising the vector and a kit comprising the isolated nucleotide sequence (emphasis added).

The claims encompass any isolated nucleic acid molecule that encodes a full-length mutant microbial purine nucleoside phosphorylase (PNP) (i.e., a mutant PNP of

any microbial species). The claims encompass any mutant microbial PNP, that is a microbial PNP that is different from the wild-type PNP of that particular species. Therefore, the claims encompass a genus of mutant PNPs that is indeterminate in size, but could possibly encompass hundreds of thousands, if not millions of different mutant microbial PNPs considering every possibly single amino acid mutation, as well as all multiple amino acid substitutions of every microbial PNP, including mutant PNPs that do not have phosphorylase activity and mutant PNPs that have yet to discovered.

The specification was thoroughly searched for a disclosure of nucleotide sequences that encode full length mutant microbial PNPs, However, the specification appears to only disclose E. coli mutant PNPs (e.g., see Table I, page 12 as well as Tables II-V). The specification does not appear to disclose any nucleotide sequence encoding a mutant PNP other than the E. coli mutant PNPs. The disclosure of mutant E. coli PNPs is not considered to be a sufficient disclosure for all mutant microbial PNPs encompassed by the claims. Since the specification does not appear to disclose a nucleotide sequence encoding a mutant microbial PNP other than a mutant E. coli PNP, the limitation "mutant microbial purine nucleoside phosphorylase" is considered new matter.

It is noted that the Applicants have indicated in the response filed 11/12/04 (see p. 9) that "numerous examples" are provided in the specification, including "22 full-length mutant microbial purine nucleoside phosphorylases" such as those in Tables I-V (see p. 9 of the response). IT is respectfully pointed out that all of the mutations disclosed in the specification, including Tables I-V are mutant E. coli PNPs. There does not appear to be a single disclosure of a mutant PNP other than the 22 mutant E. coli PNPs disclosed in Table I.

Claims 1, 2, 6, 7 and 9-33 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> An isolated nucleotide sequence that encodes a mutant E. coli purine nucleoside phosphorylase wherein said mutant E. coli purine nucleoside phosphorylase comprises the amino acid sequence that is any one of the following: (1) SEQ ID NO: 2, (2) SEQ ID NO: 2 wherein the amino acid at position 65 is methionine and wherein the amino acid at position 180 is aspartic acid, (3) SEQ ID NO: 4, and (4) SEQ ID NO: 4 wherein the amino acid at position 157 is leucine.
>
> As well as:
>
> An isolated nucleotide sequence comprising SEQ ID NO: 1 or SEQ ID NO: 3.
>
> (Including a vector and cell comprising the above isolated nucleotide sequences)

Does not reasonably provide enablement for the full scope encompassed by the claims. Specifically, the specification does not provide an enabling disclosure for an isolated nucleotide sequence that encodes a microbial purine nucleoside phophorylase other than those indicated above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to an isolated nucleotide sequence comprising a coding sequence for a full length mutant microbial purine nucleoside phosphorylase (PNP) having an amino acid substitution, wherein the mutant PNP has different biological activity than a wild type microbial PNP, as well as a vector comprising the isolated nucleotide sequence, a host cell comprising the vector and a kit comprising the isolated nucleotide sequence.

The breadth of the claims

The claims, as written, are very broad and encompass any isolated nucleotide sequence comprising a coding sequence for a full length mutant microbial purine nucleoside phosphorylase (PNP) having an amino acid substitution, wherein the mutant PNP has different biological activity than a wild type microbial PNP. The claims encompass nucleotide sequences that encode mutant microbial PNPs that "have different biological activity than a wild type microbial purine nucleotide phosphorylase", including enzymes that have PNP activity that is greater, as well as less than the activity of the wild type enzyme and include PNPs that are non-functional or have a completely different function than the wild type enzyme.

The state of the prior art (predictability)

No full-length mutant microbial PNPs were identified in the prior art. It is acknowledged that the prior art does teach a number of wild type microbial PNPs including: E. coli PNP, Aspergillis and Pencillium PNP, Salmonella typhimurium PNP,

and Bacillus subtilis PNP (NOTE: the specification acknowledges these microbial PNPs as well, see p. 5 lines 13-17). However, the prior art does not appear to teach any mutant forms of these microbial PNPs. Therefore there is no indication that full length mutant microbial PNPs that retain PNP function and have a activity different from their wild type counter part, other than E. coli PNP mutations, exist.

Working Examples and Guidance in the Specification

As indicated above, the specification discloses 22 different full-length mutant E. coli PNPs (e.g., see Table I). The specification does not disclose any full-length mutant microbial PNPs other than the 22 mutant E. coli PNPs (i.e., there are no non-E. coli mutations disclosed). Furthermore, with respect to the 22 E. coli mutations disclosed in the specification, it appears that only four specific mutations are functional PNPs: the M65V, A157L, A157V and E180D mutations (see Table I, p. 12). With respect to the functional activity of the disclosed mutant E. coli PNPs, Table I (p. 12) indicates that the negative control cell (i.e., a cell that is not transfected with a vector expressing a PNP) had an activity that is 0.8% of the activity of a cell transfected with the a vector encoding the wild-type E. coli PNP (i.e., the positive control). As such, the PNP activity of cell that does not express a PNP is 0.8. Looking at the PNP activity of each of the disclosed mutants, only the M65V, A157L, A157V and E180D mutations have PNP activity that is significantly higher than the negative control. The activity of the other mutations does not appear to be significantly different from the negative control, indicating that these mutations are not functional mutations.

Quantity of Experimentation

With respect to the non-E. coli mutant PNPs, considering that the claims encompass a genus of mutant microbial PNPs that includes thousands (and possibly millions of different mutant PNPs) in view of the fact that there is no indication or guidance provided in the specification with respect to mutant microbial PNPs other than the indicated mutant E. coli PNPs, additional experimentation would be necessary in order to determine which amino acids of the PNP for each species could be mutated such that the mutant PNP as a functional PNP. Furthermore, with respect to mutant E. coli PNPs, considering that the specification only discloses the M65V, A157L, A157V and E180D mutations as functional PNPs and further discloses data indicating that the other E. coli PNP mutations are non-functional, additional experimentation would be required in order to determine which mutations other than the M65V, A157L, A157V and E180D mutations would be functional PNPs. Considering that (1) the E. coli PNP is 239 amino acids in length, (2) the claims encompass substitution of a single amino acid as well as substitution of multiple amino acids and (3) each amino acid can be substituted with any one of the 19 other amino acids; the number of mutations that would have to be tested to determine which mutations would result in functional PNPs is enormous. For instance, making a single amino acid substitution in each of the 239 amino acids would require testing 4541 different single amino acid mutations (239x19=4541). Furthermore, to identify the number of substitutions that must be tested wherein the mutant comprises multiple substitutions, the following formula is used:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where **N** is the number of possible sequences, **X** is the number of different amino acids residues that can be substituted (19), L is the length of the reference sequence (239), **n** is the maximum number of residues that can be substituted relative to the reference sequence (e.g., 24 for 90% identity to wild-type).

The first term gives the number with one substitution, the second with two substitutions and so on to the number with n substitutions. The last term can be simplified for calculation to:

$X^n L! / n! (L-n)!$

The number of amino acid sequences that are 90% identical to the 239 amino acid wild type sequence (note that the claims are not limited to sequences that are 90% identical to the wild-type E. coli PNP), the number of possible sequences having 24 amino acid substitutions relative to the wild-type E. coli PNP (24=~90% of 239) is approximately 28×10^{43}, a number that certainly indicates an undue amount of additional experimentation is required.

Level of the skill in the art

The level of the skill in the art required to make and use the claimed invention is deemed to be high, as the ordinary artisan would normally have a Masters or Ph.D. degree in the field of Molecular Biology.

Conclusion

Considering the nature of the invention, the breadth of the claims, the state of the prior art, the limited amount of working examples and guidance provided (including the disclosure indicating that not all mutant E. coli PNPs are functionally active), and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use

the claimed invention. The amount of additional experimentation required to perform the broadly claimed invention is, in fact, undue.

It is noted that the specification has disclosed four specific mutant E. coli PNPs which are functional (M65V, A157L, A157V and E180D). Therefore, limiting the claims to an isolated nucleotide sequence that encodes any of these four specific mutants (e.g., as indicated above) would obviate this rejection.

Allowable Subject Matter

Claims 54 and 56 are allowed.

Response to Arguments

Applicant's arguments filed 11/12/04 have been fully considered but they are not fully persuasive.

With respect to the rejection of claims under 35 U.S.C. 101, 35 U.S.C. 112, second paragraph and 35 U.S.C. 112, first paragraph (as set forth in the previous Office Action), the amendment and/or arguments are persuasive and the indicated previous rejections are withdrawn.

It is noted that new grounds of rejection under 35 U.S.C. 112, second paragraph and 35 U.S.C. first paragraph (written description) are set forth. These new rejections are necessitated by the amendment.

With respect to the rejection of claims under the previous 35 U.S.C. 112, first paragraph rejection, applicants arguments are partially, but not fully persuasive.

Applicants argue, that the specification discloses 22 different full-length mutant microbial PNPs (e.g., see p. 7 of the response). It is respectfully pointed out that the specification only discloses 22 different mutant E. coli PNPs and does not disclose any non E. coli mutant microbial PNPs. Furthermore, the new limitation "mutant microbial PNP" is not found anywhere in the specification (as indicated above in the New Matter rejection). Since the specification does disclose four specific mutations of E. coli PNP that are functionally active, the enablement rejection has been amended to adjust for the four specific mutant E. coli PNPs that are disclosed and have been shown to be functionally active. The specific mutant E. coli PNPs that are enabled by the specification are the E. coli M65V, A157L, A157V and E180D mutants. Amending the pending claims such that they are limited to these specific E. coli PNP mutations would obviate the instant rejection.

With respect to the New Matter rejection above, it is noted that the applicants have not explicitly indicated where in the specification disclosure of an isolated nucleotide sequence encoding a mutant microbial PNP (other than the E. coli mutants) can be found. Applicants are asked to identify by page and line number where support for the new limitation can be found.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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